REMARKS

Applicant notes with appreciation the detail and thoroughness embodied in Paper No. 20080428 and the opportunity to distinguish the pending claims over the prior art of record. Applicant further notes with appreciation acceptance of the Information Disclosure Statement submitted on November 19, 2007 and acceptance of the drawings submitted March 30, 2006.

With entry of this amendment, claims 1-7, 9, 10, 13-16, 18, 21, 23, and 26-30, remain pending, with claims 24 and 32 being canceled. Claims 1 and 26 are amended as per Examiner's suggestion to recite that the pyrophosphate is inorganic pyrophosphate, which has proper antecedent basis in the claims. No new matter is introduced by way of amendment. Claims 4 and 29 are amended to recite that the enzyme is incubated with the purified reaction product. These amendments are fully supported by the specification as filed *inter alia* page 3, lines 23-27. As such, no new matter is introduced by way of amendment. Claim 30 is currently amended as per Examiner's suggestion to recite "the pyrophosphate removing enzyme" such that this phrase has proper antecedent basis. As such, it is submitted that no new matter is introduced by way of this amendment.

In the Office Action of May 9, 2008 the specification is objected to because of informalities.

Claim 24 is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. As this claims is canceled, the objection is now moot.

Claims 1-7, 9, 10, 13-16, 18, 21, 23, 24, 26-30, and 32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-7, 9, 10, 13-16, 21, and 26-30 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US

Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523). Claims 18, 23, and 24 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) and further in view of Jack et al. (WO 01/23411 A2).

Claim 32 is canceled rendering the rejection rendering moot the rejection of this claim under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) and further in view of Jack et al. (WO 01/23411 A2).

Remarks regarding the rejection of claims 1-7, 9, 10, 13-16, 18, 21, 23, 24, 26-30, and 32 under 35 U.S.C. § 112, second paragraph, indefiniteness.

Withdrawal of the rejection of claims 1-7, 9, 10, 13-16, 18, 21, 23, 24, 26-30, and 32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention is respectfully requested in light of the amendments to claims 1, 4, 26, 29, 30, and the cancelation of claim 32.

Remarks directed to the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523).

Withdrawal of the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) is respectfully requested for at least the following reasons. Kwok et al. in view of Tabor et al. fails to teach or suggest all elements in the claims, or provide motivation and a reasonable expectation of success from the combination.

Standards for Obviousness Rejection and Response

It is Applicant's understanding that the form and substance of rejections under 35 U.S.C. §103(a) are currently governed by guidelines articulated in the Federal Register, 2007, Vol. 72, No. 195, 56525-56534. These guidelines require a factual inquiry, resolution of ordinary skill in the art to which the invention pertains, and an explicit recitation of the rationale for the rejection as selected from among seven possible bases (identified in the Federal Register with letters A-G). The basis for Applicant's reply is also provided within the Federal Register guidelines.

Graham Factual Findings and Response Thereto

The rejection relies on Kwok et al. teaching a product of a nucleic acid synthesis reaction comprising a nucleic acid template and a quantity of inorganic pyrophosphate; purifying the nucleic acid synthesis product to obtain a purified reaction product; combining the purified reaction product with a primer, a labeled terminator nucleoside, and a polymerase; and extending the primer by addition of the labeled terminator in a single base extension reaction.. (Paper No. 20080428, page 5.) Regarding independent claims 2 and 27, Kwok et al. is cited as teaching residual primers and nucleotides in the PCR amplification product. Id. Regarding claims 3 and 28, Kwok et al. is cited as teaching "incubating the nucleic acid synthesis product with an exonuclease and an alkaline phosphatase to degrade the residual primers and nucleotides and then inactivating the enzymes." Id. Regarding claims 5, 6, and 30, Kwok et al. is cited as teaching enzyme inactivation. (Paper No. 20080428, page 6.) Regarding claims 9 and 10, Kwok et al. is cited as teaching detection by fluorescence polarization. Id. Regarding claim 13, Kwok et al. is cited as teaching bacterial alkaline phosphatase. Id. Regarding claim 14, Kwok et al. is

cited as teaching shrimp alkaline phosphatase. Id. Finally, regarding claim 21, Kwok et al. is cited as teaching that all the steps are performed in a single reaction container. Id.

Applicant respectfully traverses the assertion that Kwok et al. teach or suggest the claimed step of producing a purified reaction product. The cited section of Kwok et al. teaches degradation of the PCR primer and dNTPs by the use of shrimp alkaline phosphatase and *E. coli* exonuclease I. (column 10, lines 48-58.) This "purification step" results in consumption of the primer and dNTPs to produce a post-PCR reaction solution operable for the subsequent genotyping reaction taught therein. However, production of a purified reaction product as in subject claim 1 does not represent degradation of the PCR primers and dNTPs. Instead the purified reaction product represents amplified product of the nucleic acid synthesis reaction with the resulting inorganic pyrophosphate removed. The specification teaches that a purified reaction product is the product of a nucleic acid synthesis reaction incubated with an inorganic pyrophosphatase to "decrease the quantity of pyrophosphate thereby yielding a purified reaction product." (page 5, lines 4-5.) Thus, a purified amplification product has inorganic pyrophosphate removed from the reaction system. Removal of inorganic pyrophosphate from the reaction system is not accomplished by the reaction of Kwok et al. because neither shrimp alkaline phosphatase nor *E. coli* endonuclease I are capable of removing inorganic pyrophosphate from the solution.

Moreover, the cited reaction in Kwok et al. at column 10, lines 48-58 is recognized in Paper No. 20080428 at page 5 as independent from a purification reaction as the rejection asserts that the incubation of "a nucleic acid synthesis product with an exonuclease and an alkaline phosphatase to degrade the residual primers and nucleotides and then inactivating the enzymes" is a separate step representing the elements claimed in instant claims 3 and 28. As such, Kwok et

al. fails to teach or suggest purifying the nucleic acid synthesis product to obtain a purified reaction product.

Applicant further traverses the assertion that Kwok et al. teach inactivation of an inorganic pyrophosphatase. Applicant recognizes that Kwok et al. teach enzyme inactivation. However, the enzymes being inactivated are shrimp alkaline phosphatase or *E. coli* exonuclease I. In contrast, claims 6 and 30 claim the step of inactivating the inorganic pyrophosphatase or the pyrophosphate removing enzyme. As neither shrimp alkaline phosphatase nor *E. coli* exonuclease I are an inorganic pyrophosphatase or a pyrophosphate removing enzyme, the inactivations of claims 6 and 30 are neither taught nor suggested by Kwok et al.

Finally, Applicant traverses the assertion that Kwok et al. teach that the steps are performed in a single reaction tube. Kwok et al. at column 3, line 65 to column 4, line 5 is not understood by Applicant as suggesting a single reaction chamber. It is requested that Examiner be more explicit in highlighting the language in this section of Kwok et al. that is asserted to teach a single reaction chamber. Moreover, examination of the Kwok et al. reference indicates that multiple reaction chambers are used. For example, column 10, lines 60-64 state that "[a]fter PCR primer and dNTP degradation, aliquots of the PCR mixture (10 μL) were distributed into two new reaction tubes for parallel assays." (emphasis added) As such, Applicant submits that Kwok et al. fail to teach or suggest a single reaction chamber.

To bolster the failing of Kwok et al. in teaching "incubating the nucleic acid synthesis product or the purified reaction product with an inorganic pyrophosphatase or a pyrophosphate removing enzyme to reduce the quantity of inorganic pyrophosphate present in the nucleic acid synthesis product or the purified reaction product," (Paper No. 20080428, page 6) Tabor et al. is cited as teaching "the inclusion of an inorganic pyrophosphatase in the amplification reaction."

Id. Further, Tabor et al. is cited as teaching that "inhibiting pyrophosphorolysis improves the efficiency of the reaction [and] these benefits are also applicable to primer extension reactions and sequencing reactions." (Paper No. 20080428, page 7.)

Resolution of One of Ordinary Skill in the Art

Part of the Graham factual inquiry requires an indication as to level of ordinary skill in the art to which the invention pertains. Within the outstanding Office Action, as such, it is respectfully requested that the level of ordinary skill in the art be stated with greater specificity as the present invention is submitted to require skills beyond those imparted to a single person of ordinary skill in the art. Upon identification of level of ordinary skill in the art, Applicant reserves the right to make of record additional declarations provided under 37 CFR 1.132 detailing how particular claimed aspects are beyond the scope of various such professional individuals such as biological scientists.

Rationale for Obviousness

The Federal Register obviousness examination guidelines detail seven rationales. These rationales are reproduced below.

> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

> (E) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

(Federal Register, Vol. 72, No. 195, 57529).

The basis of the rejection is that "[i]t would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Tabor to the method taught by Kwok." (Paper No. 20080428, page 7.) Motivation for combining the "PCR and primer extension steps" of Kwok et al. with the inorganic pyrophosphatase of Tabor et al. is provided by the teaching of Tabor et al. "that inorganic pyrophosphatase degrades inorganic pyrophosphate produced by these reactions, thereby improving the efficiency of the reaction by inhibiting the detrimental pyrophosphorolysis reaction." Id. A person having ordinary skill in the art is cited to have reasonable expectation of success because Tabor et al. teach that "inorganic pyrophosphatase was commercially available." Id.

The explanations articulated in Paper No. 20080306, lead Applicants to the assumption that the rationale for obviousness corresponds to rationale (G) of the KSR obviousness examination guidelines namely that the Examiner has found some teaching, suggestion, or motivation in the Kwok et al. and Tabor et al. that would have led one of ordinary skill to combine the Kwok et al. and Tabor et al. teachings to arrive at the claimed invention. In the event that Applicant's assumption as to the rationale for the rejection is incorrect, it is respectfully requested that the undersigned attorney of record be contacted at the earliest possible

convenience so that a response may be provided consistent with the implicit rationale for the finding of obviousness. The requirements for an obviousness rejection based on this rationale are listed on page 57534 of the Federal Register, Vol. 72, No. 195 and are reproduced below.

> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (2) a finding that there was reasonable expectation of success; and
>
> (3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Implicit in this rationale is a showing that Kwok et al. and Tabor et al. when combined produce the claimed invention. This is fully in line with precedent not changed by the holding in KSR, that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Moreover, "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some rational underpinning to support the legal conclusion," and "this analysis should be made explicit." KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1741 (2007).

The CAFC has further interpreted KSR as applied to the biological arts to require an explicit showing that the prior art would have suggested making the specific modifications necessary to achieve the claimed invention. This standard was affirmed in Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., where the Federal Circuit continued application of the teaching, suggestion, and motivation test "flexibly applied" so as to require that any *prima*

facie case of obviousness must be accompanied by an explicit showing where the relied on prior art provided the requisite teaching, suggestion, or motivation. 520 F.3d 1358, 1364-65 (Fed. Cir. 2008). Applicant submits that the prior art of record fails to provide, explicitly or inherently, any teaching, suggestion, or motivation that would lead a person having ordinary skill in the art to the instantly claimed invention.

Substantive Distinctions between Prior Art Reference Combination and Claimed Invention

The teaching of Kwok et al. alone or in combination with Tabor et al. fails to teach or suggest numerous elements of the pending claims.

Regarding independent claims 1 and 26, as highlighted above, Applicants respectfully traverse the assertion that Kwok et al. teach or suggest incubating a product of a nucleic acid synthesis reaction with an inorganic pyrophosphatase to yield a purified reaction product. Further, the teaching of Tabor et al. also fails to teach or suggest this element of the claims.

Tabor et al. teaches adding an inorganic phosphatase to a PCR amplification reaction. The product of this PCR amplification reaction is representative of the product of a nucleic acid synthesis reaction in the subject claims. Motivation to combine an inorganic pyrophosphatase in a nucleic acid amplification reaction is provided by Tabor et al. and captured in the rejection as arising from a teaching of Tabor et al. that inclusion of inorganic pyrophosphatase improves "the efficiency of the reaction by inhibiting detrimental pyrophosphorolysis reaction." (Paper No. 20080428, page 7.) However, simply because an inorganic pyrophosphatase may improve the efficiency of a PCR reaction does not teach or suggest to a person having ordinary skill in the art using an inorganic pyrophosphatase to treat a product of a nucleic acid synthesis reaction as required by the subject claims. These two steps in the inventive process are separate and distinct. The subject claims require incubating a product of a nucleic acid synthesis reaction with an

inorganic pyrophosphatase. In contrast, Tabor et al. teach using an inorganic pyrophosphatase in a nucleic acid synthesis reaction, not as a purification step applied to the product of such a reaction.

The distinction between the two steps is recognized in Paper No. 20080428 at page 7 which finds motivation in Tabor et al. to "include an inorganic pyrophosphatase in the PCR amplification and primer extension steps of the method taught by Kwok." Assuming, *arguendo*, that this motivation is provided by Tabor et al., a motivation to combine inorganic pyrophosphatase in a PCR reaction does not provide motivation to use inorganic pyrophosphatase in a purification step of the product of a PCR reaction as required by the subject claims. As such, no teaching of Tabor et al. provides suggestion or motivation for incubating the product of nucleic acid synthesis reaction with an inorganic pyrophosphatase.

Secondly, the requirements under rational (G) require a showing of a reasonable expectation of success. This showing must be both rational and more than a mere conclusory statement. "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some rational underpinning to support the legal conclusion." KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1741 (2007). The articulated underpinning for a reasonable expectation of success in Paper No. 20080428 at page 7 is that "Tabor taught that inorganic pyrophosphatase was commercially available." The commercial availability of a reagent does not provide motivation for its use in an inventive method. "As is clear from cases such as Adams, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 127 S. Ct. at 1741 (citing United States v. Adams, 383 U.S. 39 (1966)). Similarly, a reasonable expectation of success is not provided simply because a reagent is available on the market place.

Cumin is also commercially available, but this does not suggest that addition of cumin to a PCR reaction will boost its efficiency. Thus, there is no rational underpinning for a finding of reasonable expectation of success simply because a reagent is commercially available. As such, it is submitted that no reasonable expectation of success is provided or articulated from the teaching of Tabor et al.

In light of the foregoing remarks, Applicant submits that independent claims 1 and 26 are nonobvious over the prior art of record in that the combination of Kwok et al. and Tabor et al. fails to teach or suggest all elements of the pending claims, or provide motivation or a reasonable expectation of success for all elements of the pending claims. Similarly, dependent claims 2-7, 9, 10, 13-16, 21, and 27-30 are submitted to be patentable and nonobvious as dependent from a nonobvious base claim. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Finally, the cited teaching of Tabor et al. fails to correct the aforementioned deficiencies of Kwok et al. to teach or suggest inactivation of an inorganic pyrophosphatase or a pyrophosphate removing enzyme. As such, it is submitted that claims 6 and 30 possess an independent basis of patentability. Similarly, Kwok et al. and Tabor et al. fail to teach or suggest performing all the claimed steps in a single reaction chamber as required by subject claim 21. As such, it is submitted that claim 21 possess an independent basis of patentability.

Additional bases of patentability exist, and Applicant reserves the right to make these of record in the course of prosecution as necessary.

In light of the foregoing remarks, withdrawal of the rejection of claims 1-7, 9, 10, 13-16, 21, and 26-30 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. in view of Tabor et al. is respectfully requested.

Remarks directed to the rejection of claims 18, 23, and 24 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2).

Withdrawal of the rejection of claims 18, 23, and 24 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2) is respectfully requested.

Jack et al. is cited as teaching "methods and compositions for improving the incorporation of chain terminating nucleotides by DNA polymerases," and that "dye-labeled acyclo-NTPs are more readily incorporated by Family B archaeon DNA polymerases, such as Vent, Pfu, Deep Vent, and 9N, than dye-labeled ddNTPs." (Paper No. 20070428, page 8.)

Motivation for combining Jack et al. with Kwok et al. and Tabor et al. is asserted as provided by a teaching of Jack et al. "that dye-labeled acyclo NTPs were more efficiently incorporated by a Family B archaeon DNA polymerase than ddNTPs." (Paper No. 20070428, page 9.) Particular motivation is asserted as provided by a teaching of Jack et al. that substituting dye-labeled acylo NTPs and a Family B archaeon DNA polymerase produce "more efficient terminator incorporation[,] reduced costs, decreased background, and improved sensitivity." Id.

A reasonable expectation of success is asserted as resulting from the teaching of Jack et al. that the dye-labeled acylo NTPs and Family B archaeon DNA polymerase "were suitable for single base extension methods, such as the single base extension method taught by Kwok." Id.

However, no teaching of Jack et al. corrects the aforementioned deficiencies in Kwok et al. or Tabor et al. in teaching incubating a product of a nucleic acid synthesis reaction with an inorganic pyrophosphatase to yield a purified reaction product as required by independent claim 1 from which claims 18, 23, and 24 depend. As such, the cited prior art combination of Kwok et

al., Tabor et al, and Jack et al. fails to teach or suggest all elements of the claimed invention as required for any finding of obviousness.

Additional bases of patentability exist, and Applicant reserves the right to make these of record in the course of prosecution as necessary.

In light of the forgoing remarks, withdrawal of the rejection of claims 18, 23, and 24 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2) is respectfully requested.

Remarks directed to the rejection of claim 32 under 35 U.S.C. § 103(a) as being unpatentable over Kwok et al. (US Pat. No. 6,180,408 B1) in view of Tabor et al. (US Pat. No. 5,498,523) in further view of Jack et al. (WO 01/23411 A2).

In the interest of furthering prosecution and not by way of admission as to lack of patentability, claim 32 is canceled thereby rendering moot the outstanding rejection.

SUMMARY

Claims 1-7, 9, 10, 13-16, 18, 21, 23, 24, 26-30, and 32 are currently pending in the application. All pending claims are submitted to be in allowable form and directed to patentable subject matter. Reconsideration and withdrawal of the rejections is, thus, respectfully requested.

Should the Examiner have any questions, Applicant's attorney may be reached at the telephone number given below.

Date: August 4, 2008

Respectfully submitted,

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